REMARKS

Applicants have amended Claims 1, 7, 8, and 87; have canceled Claim 5; and have added new Claims 95-96 herein. Enabling support for the amendments to Claim 1, 8, and 87 can be found in the application as filed (*e.g.*, original claims 2, 6, and 7), and enabling support for new Claims 95-96 can be found in the application as filed (*e.g.*, original Claims 1, 9, and 10). Therefore, no new matter is contained in the amendments and additions. Reconsideration of the present application and allowance of pending Claims 1-4, 6-52, and 87-96 is respectfully requested in view of the amendments and following remarks.

I. Rejection Under 35 U.S.C. § 102(b)

The Office Action rejected Claims 1, 7, 12-18, and 23 under 35 U.S.C. § 102(b) as being anticipated by Davis *et al.* (Chemistry of Materials, 1998, Vol. 10, No. 9, pp. 2516-2524). In particular, the Office Action asserted that Davis *et al.* disclose a nanoparticle composition comprising a magnetic nanoparticle with a biocompatible coating and a targeting probe. The rejection is respectfully traversed if applied to the pending claims.

The present invention discloses compositions for use in intracellular molecular imaging that have at least three required components: 1) a magnetic nanoparticle with a biocompatible coating thereon, 2) at least one targeting probe, and 3) an intracellular delivery ligand. These nanoparticle probes provide high specificity, high sensitivity, and enhanced signal-to-noise ratio in molecular imaging. Accordingly, these nanoparticles can be used for both optical intra-cellular imaging and deep-tissue molecular imaging using MRI.

The claimed compositions require a biocompatible coating on the magnetic nanoparticles that may be, for example, dextran, dendrimers, amphiphilic polymers/bio-polymers (*e.g.*, phospholipids and peptides), polymers, surfactants or chemical compounds with chelating properties for magnetic nanoparticles or high affinity adsorption (*e.g.*, both chemisorption or physical adsorption) on the surface of magnetic nanoparticles, silicon oxide, silica, silica-PEG, mesoporous structures (silica or polymers or their combinations) for encapsulation of nanoparticles, or combinations thereof. *See* page 14, paragraph [046] to page 15, paragraph [047]. As discussed previously, examples of targeting probes include, for example, a nucleic

acid, a polypeptide, an antibody or fragment thereof, a high affinity ligand, a peptide, and an aptamer. The targeting probe facilitates the detection of a particular intracellular molecule and/or its expression levels. *See* pages 18-32. As also discussed previously, the intracellular delivery ligand facilitates the delivery of the nanoparticle across a cellular membrane or additionally across an intracellular organelle membrane. *See* page 15, paragraph [048].

In order for a reference to be anticipatory, the reference must teach each and every element of the claimed invention. *See* MPEP § 2131. Applicants respectfully submit that Davis *et al.* do not anticipate the present invention because they fail to teach every element of the present invention. Davis *et al.* teach the formation of fibrous composite materials that have an extended, ordered microstructure. *See* page 2516, abstract and first paragraph, and page 2517, second column, first full paragraph. In particular, Davis *et al.* teach the incorporation of preformed magnetic (Fe_3O_4) and semi-conducting (CdS) nanoparticles into bacterial filaments of *Bacillus subtilis*. The bacterial threads were dipped into a colloid of magnetite nanoparticles, resulting in the concentration of magnetite nanoparticles being located around and between the filaments of the bacterial superstructure. *See* page 2518, second column, bridging paragraph to page 2519, first paragraph. The magnetic nanoparticles taught by Davis *et al.* do not have a biocompatible coating or any other coating thereon. *See, e.g.*, page 2517, second column, last full paragraph to bridging paragraph. In addition, the magnetic nanoparticles of Davis *et al.* do not contain a targeting probe for the detection of a particular intracellular molecule or its expression levels. Moreover, Davis *et al.*'s magnetic nanoparticles also do not contain an intracellular delivery ligand that facilitates the delivery of the particles across cellular and/or intracellular organelle membranes. *See, e.g.*, page 2517, last full paragraph to bridging paragraph. By contrast, Davis *et al.*'s magnetic nanoparticles are bare nanoparticles in a colloidal preparation.

All of the pending claims require that the composition have a magnetic nanoparticle with a biocompatible coating thereon and both a targeting probe and an intracellular delivery ligand attached to the biocompatible coating. Davis *et al.* do not teach or remotely suggest the use of a biocompatible coating, a targeting probe, or an intracellular delivery ligand. Accordingly, Davis *et al.* do not anticipate or render obvious the present invention. The rejection under 35 U.S.C. § 102(b) should be withdrawn.

II. Rejection Under 35 U.S.C. § 103(a)

The Office Action rejected Claims 1, 5, 7, 9, 11-17, 19, 21-26, 36-38, 40-43, 45, 47-51, 87-91, and 93 under 35 U.S.C. § 103(a) as being unpatentable over Wunderbaldinger *et al.* (Bioconjugated Chemistry, 2002, Vol. 13, No. 2, pages 264-268). In particular, the Office Action asserted that Wunderbaldinger *et al.* disclose that the Tat peptide directs enhanced clearance and hepatic permeability of magnetic nanoparticles (*i.e.*,Tat-CLIO (crosslinked dextran coated iron oxide)). The Office Action asserted that the Tat-CLIO nanoparticles have multiple Tat peptides per nanoparticle, and that Wunderbaldinger *et al.*, therefore, disclose a nanoparticle composition comprising a magnetic nanoparticle having a biocompatible coating and a targeting probe. The rejection is respectfully traversed.

The rejection is moot with respect to Claims 1, 5, 7, 9, 11-17, 19, 21-25, 87-91, and 93 due to the cancellation of Claim 5 and the amendments to Claims 1 and 87. Amended Claims 1 and 87 are directed to nanoparticle probes in which the targeting probe is selected from the group consisting of a nucleic acid probe, an antibody, an antibody fragment, a high affinity ligand, and an aptamer.

The Patent Office bears the initial burden of establishing a *prima facie* case of obviousness. There must be a suggestion or motivation in the reference(s) to modify the reference(s); there must be a reasonable expectation of success; and the prior art reference(s) must teach all of the claim limitations. *See* MPEP § 2143. Here, the Patent Office has not met this burden because the cited reference does not teach all of the claim limitations. Claims 26, 36-38, 40-43, 45, and 47-51 all require that the claimed compositions comprise two different magnetic nanoparticle probe compositions for use in intracellular molecular imaging. Claims 26, 36-38, 40-43, 45, and 47-51 also require that both of the two different magnetic nanoparticle probe compositions have at least three required components: 1) a magnetic nanoparticle with a biocompatible coating thereon, 2) at least one targeting probe, and 3) an intracellular delivery ligand.

Wunderbaldinger *et al.* teach the use of superparamagnetic iron oxide magnetic nanoparticles with a crosslinked dextran coating and Tat peptides attached to the dextran coating. However, Wunderbaldinger *et al.* do not teach or suggest the use of a targeting probe for the

detection of a particular intracellular molecule or its expression levels. Therefore, Wunderbaldinger *et al.*'s nanoparticles do not anticipate the claimed nanoparticle probe compositions because Wunderbaldinger *et al.*'s nanoparticles do not contain each of the three required components. Furthermore, Wunderbaldinger *et al.* also do not teach or remotely suggest the use of a combination of two different magnetic nanoparticle probes, each with a biocompatible coating thereon, a different specific targeting probe, and an intracellular delivery ligand.

For at least these reasons, Wunderbaldinger *et al.* do not render obvious the presently claimed invention. Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. § 103(a) be withdrawn.

IV. Conclusion

Applicants believe that the present application, as amended, is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The foregoing is submitted as a full and complete response to the Office Action mailed February 9, 2007.

No fees are believed due at this time. However, please charge any fees that may be due, or credit any overpayment, to Deposit Account 19-5029 (Ref.: 17625-0058). In addition, if there are any issues that can be resolved by a telephone conference or an Examiner's amendment, the Examiner is invited and encouraged to call the undersigned attorney at (404) 853-8000.

Respectfully submitted,

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